

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : G01N 33/569, 33/557, A61K 39/00, C07K 14/00, C12N 15/00, 15/83		A1	(11) International Publication Number: WO 97/41440
			(43) International Publication Date: 6 November 1997 (06.11.97)
(21) International Application Number: PCT/NL97/00229		nelius, Johannes, Maria [NL/NL]; Wilhelminapark 33, NL-2012 KC Haarlem (NL).	
(22) International Filing Date: 28 April 1997 (28.04.97)		(74) Agent: SMULDERS, Th., A., H., J.; Vereenigde Octrooibureaux, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).	
(30) Priority Data: 96201145.8 26 April 1996 (26.04.96) EP (34) Countries for which the regional or international application was filed: NL et al. 96203670.3 23 December 1996 (23.12.96) EP (34) Countries for which the regional or international application was filed: NL et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicants (for all designated States except US): RIJKSUNIVERSITEIT TE LEIDEN [NL/NL]; Stationsweg 46, NL-2312 AV Leiden (NL). SEED CAPITAL INVESTMENTS (SCI) B.V. [NL/NL]; Bernadottelaan 15, NL-3527 GA Utrecht (NL).		Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(72) Inventors; and (75) Inventors/Applicants (for US only): VAN DER BURG, Sjoerd, Henricus [NL/NL]; Schuberthof 15, NL-2742 BT Waddinxveen (NL). KAST, Wybe, Martin [NL/US]; 201 Hill Road, Willowbrook, IL 60150 (US). TOES, Reinaldus, Everardus, Maria [NL/NL]; Marco Polostraat 73 III, NL-1057 WN Amsterdam (NL). OFFRINGA, Rienk [NL/NL]; Stieltjesstraat 63, NL-2313 SJ Leiden (NL). MELIEF, Cor-			
(54) Title: METHODS FOR SELECTING AND PRODUCING T CELL PEPTIDE EPITOPES AND VACCINES INCORPORATING SAID SELECTED EPITOPES			
(57) Abstract The present invention relates to the field of molecular biology and immunology. In particular it relates to vaccines and methods for providing vaccines which elicit immune responses when administered to a mammal, in particular a human. The preferred elicited immune response is a T cell response, elicited by peptide T cell epitopes. These vaccines find their application in many fields ranging from cancer treatments to treatments of prophylaxis of infectious diseases such as Aids. The present invention provides novel methods for selecting the peptide sequences from an intact antigen which will lead to a proper (T cell) immune response upon administration in a suitable vehicle. The epitopes and vaccines are, of course, also part of the present invention.			

1/14

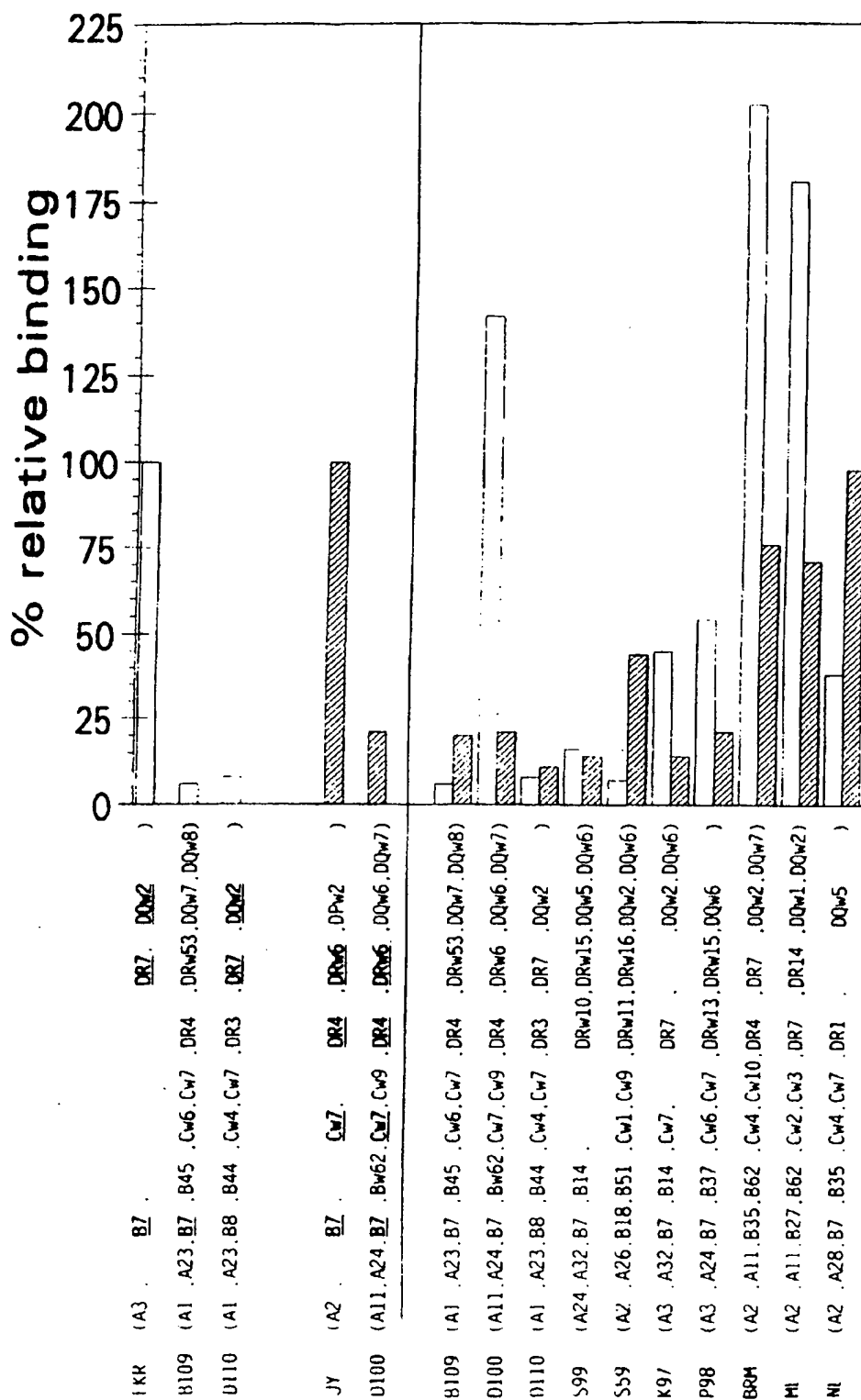


FIG. 1

2/14

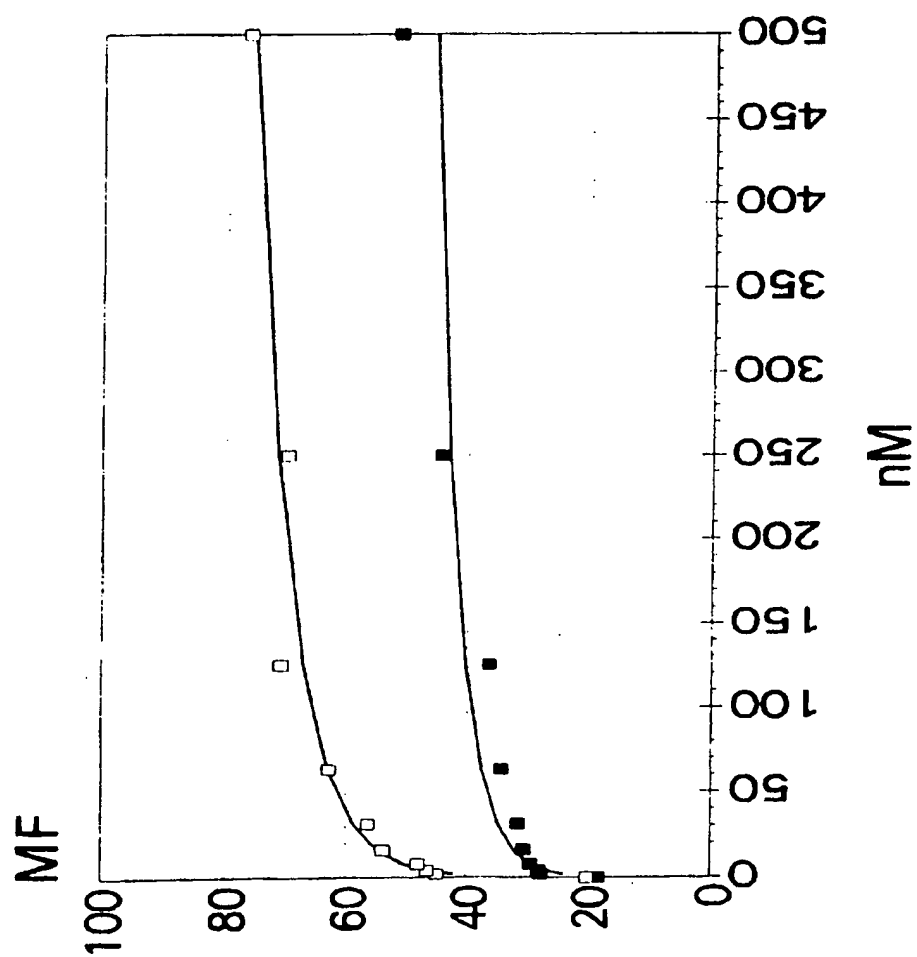


FIG. 2

3/14

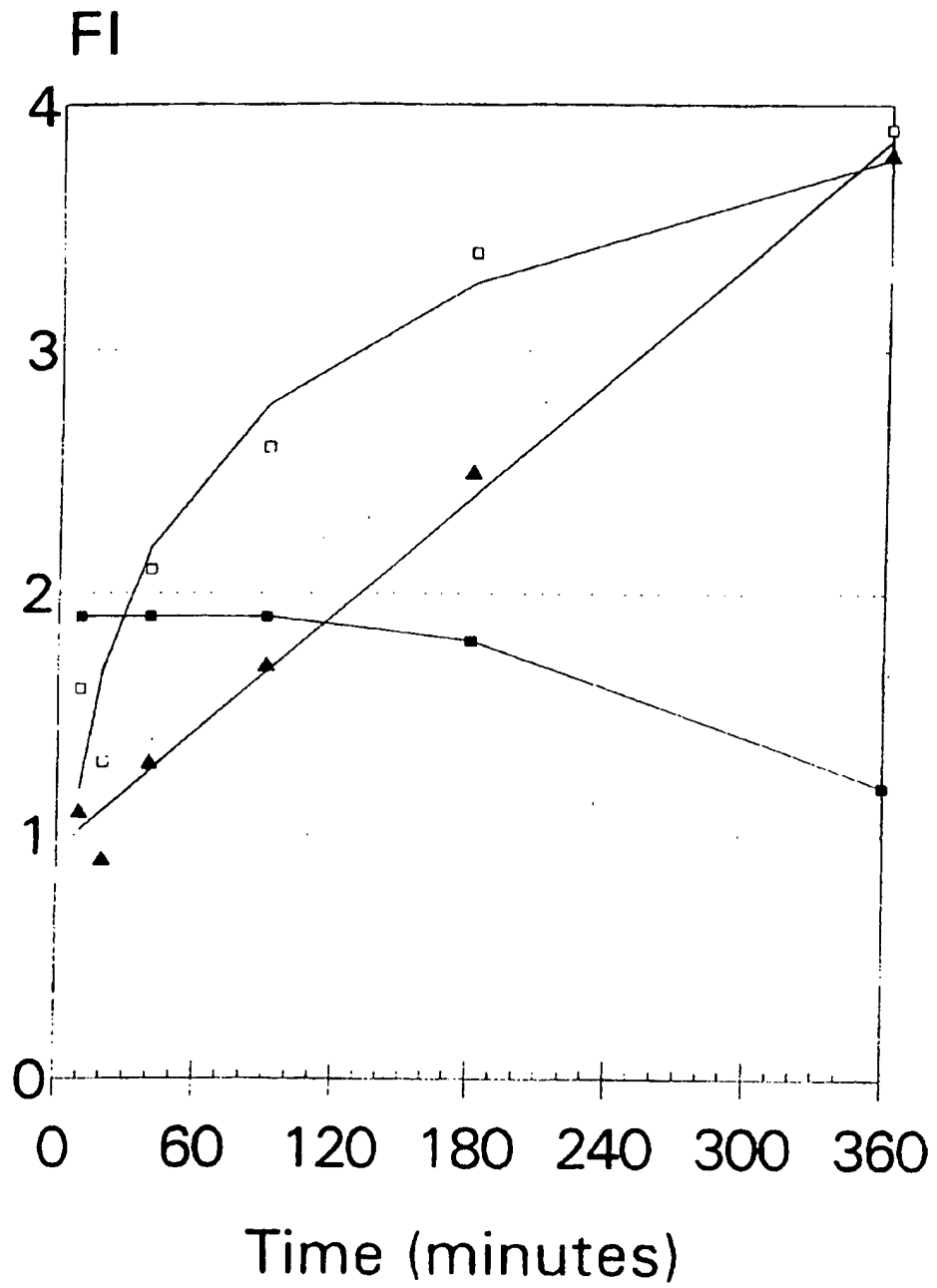


FIG. 3

4/14

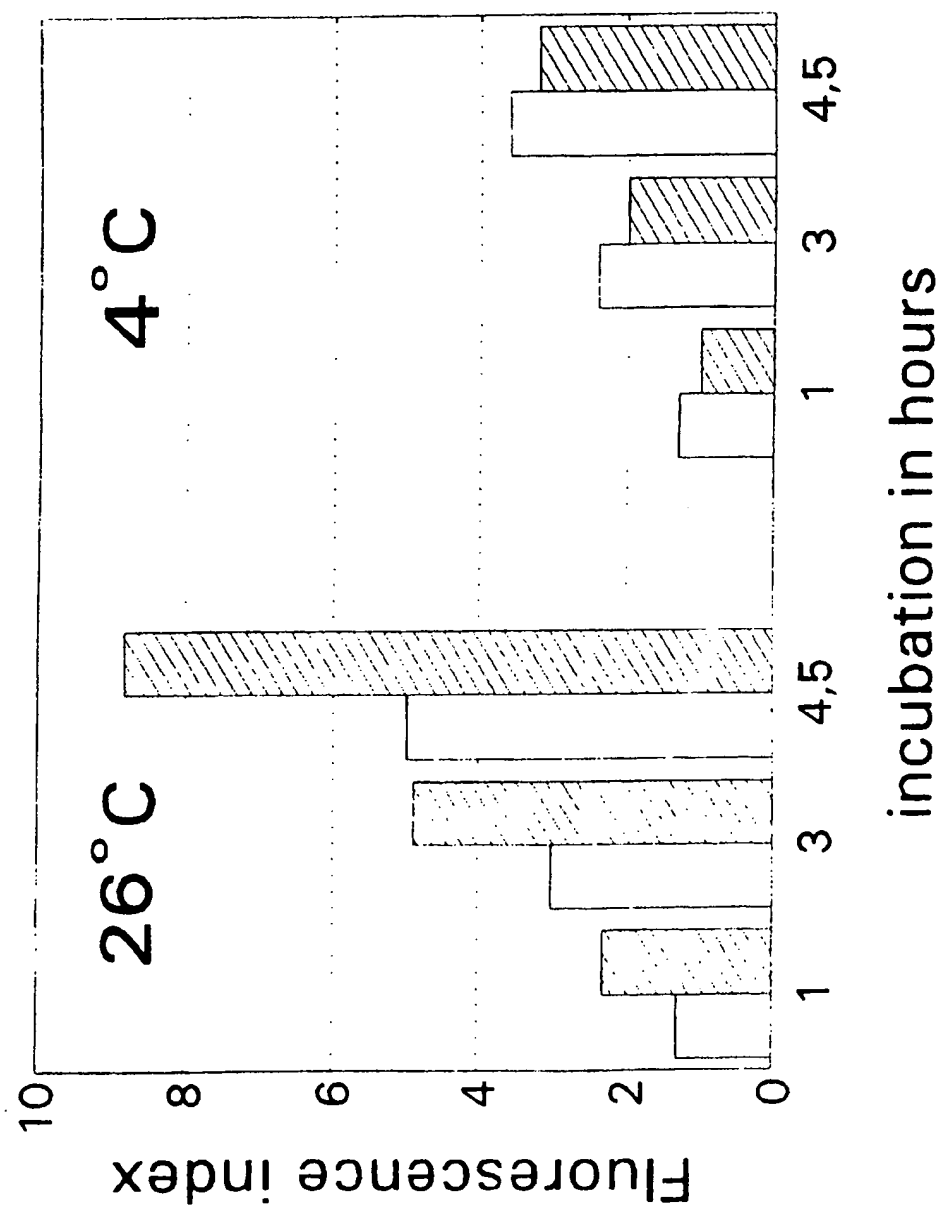


FIG. 4

5/14

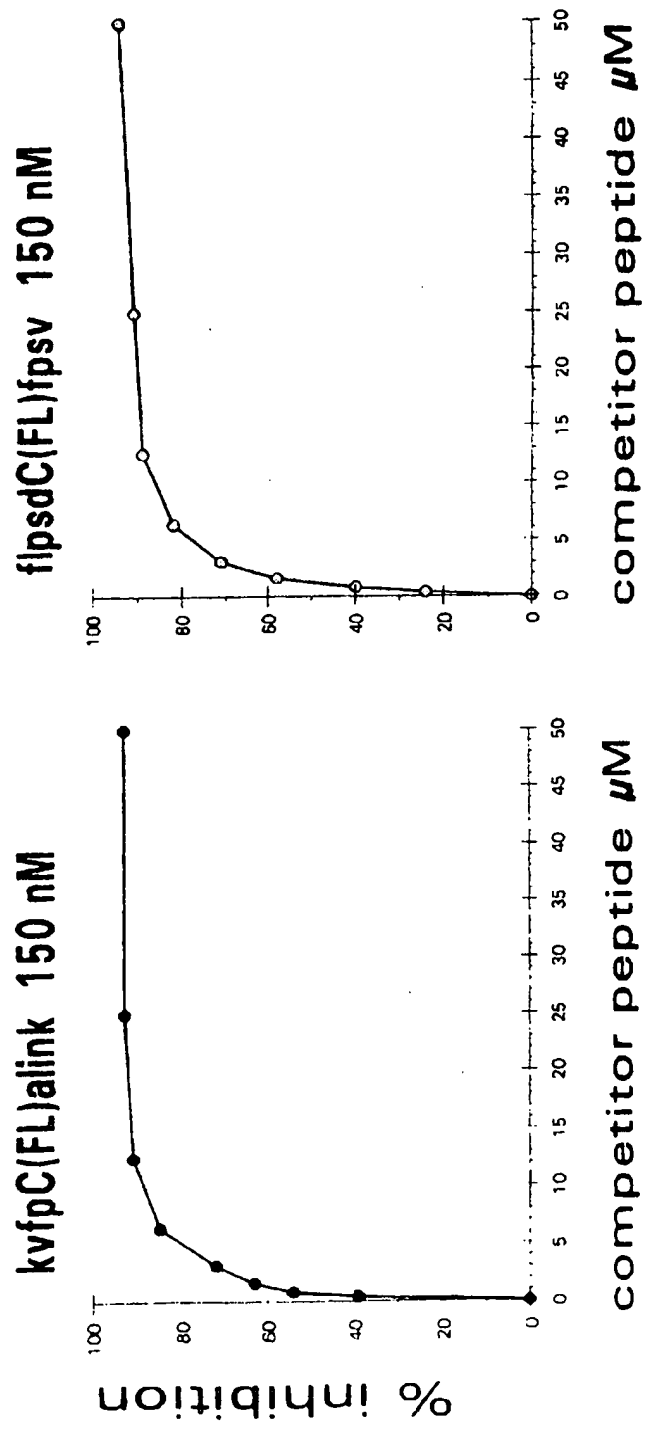


FIG. 5

6/14

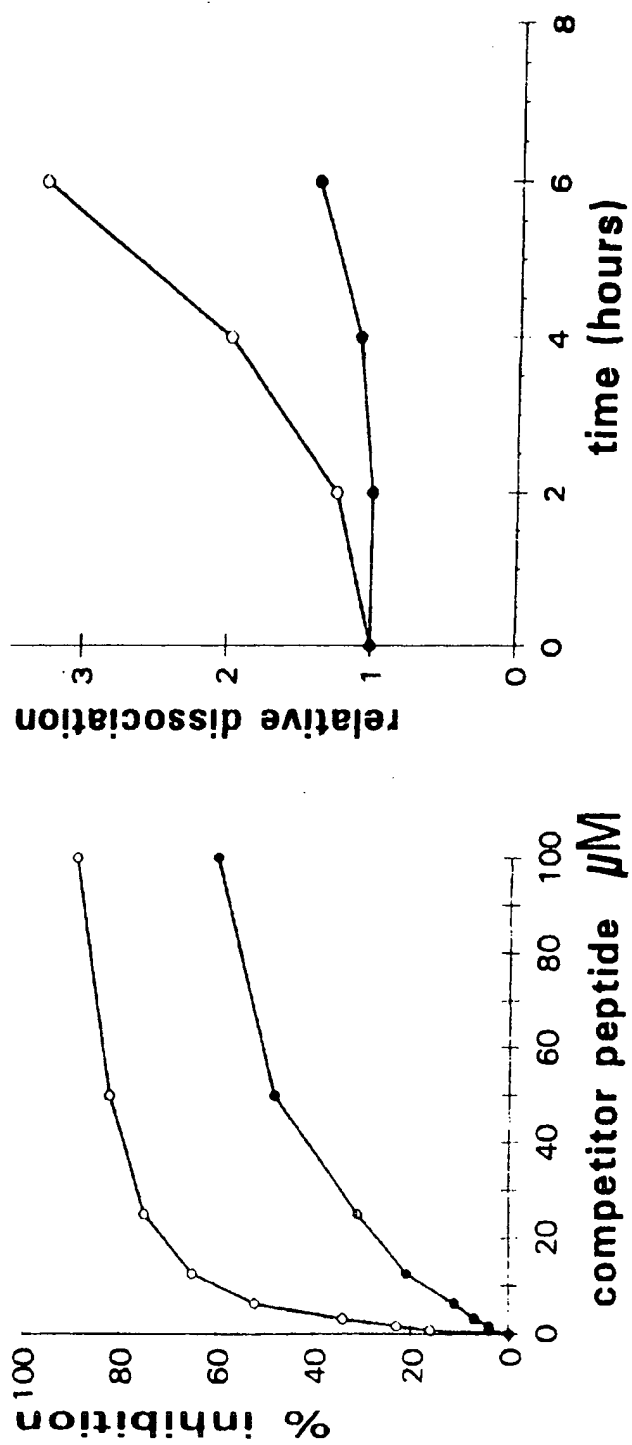


FIG. 6

7/14

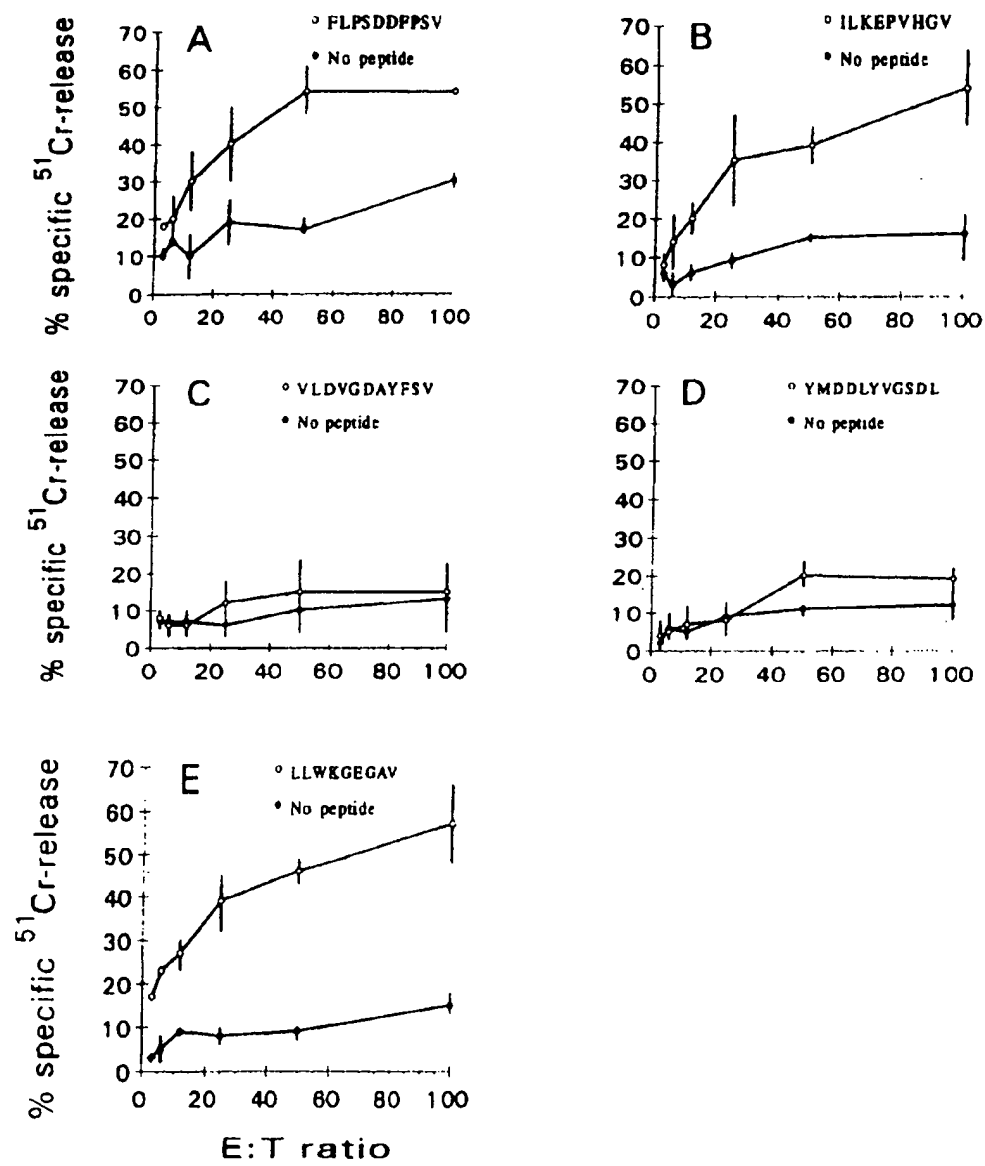


FIG. 7

Recombinant Adenoviruses carrying 'string bead' minigenes

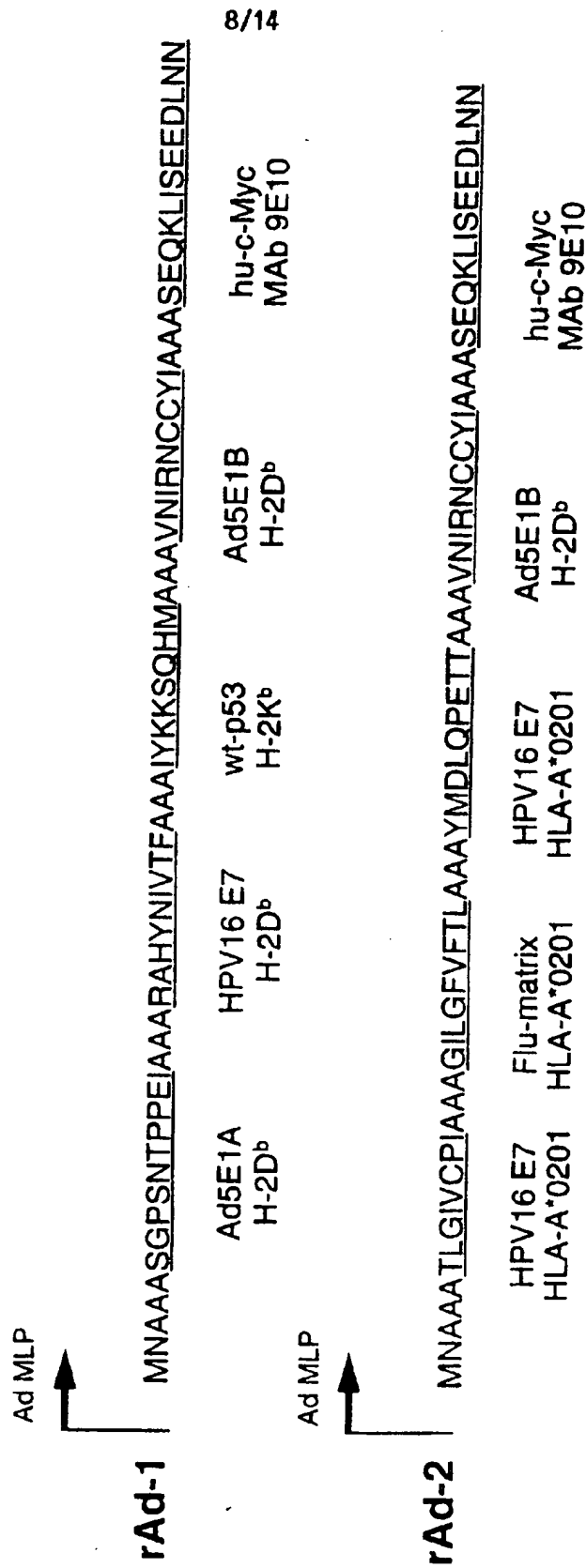
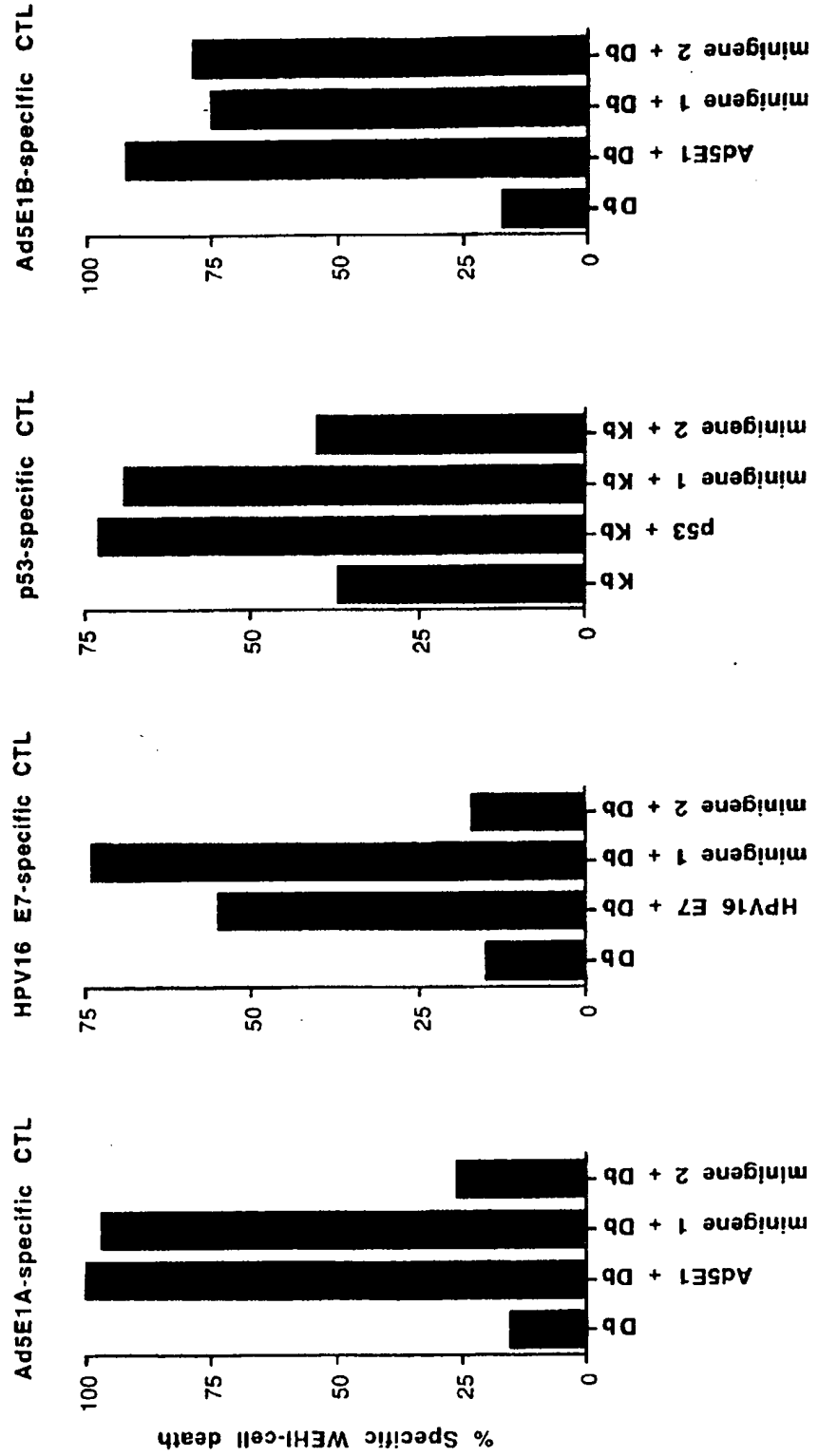


Figure 8

**CTL epitopes encoded by string-bead minigene 1
are processed and presented to tumor-specific CTL**



CTL epitopes encoded by string-bead minigene 2 are processed and presented to tumor-specific CTL

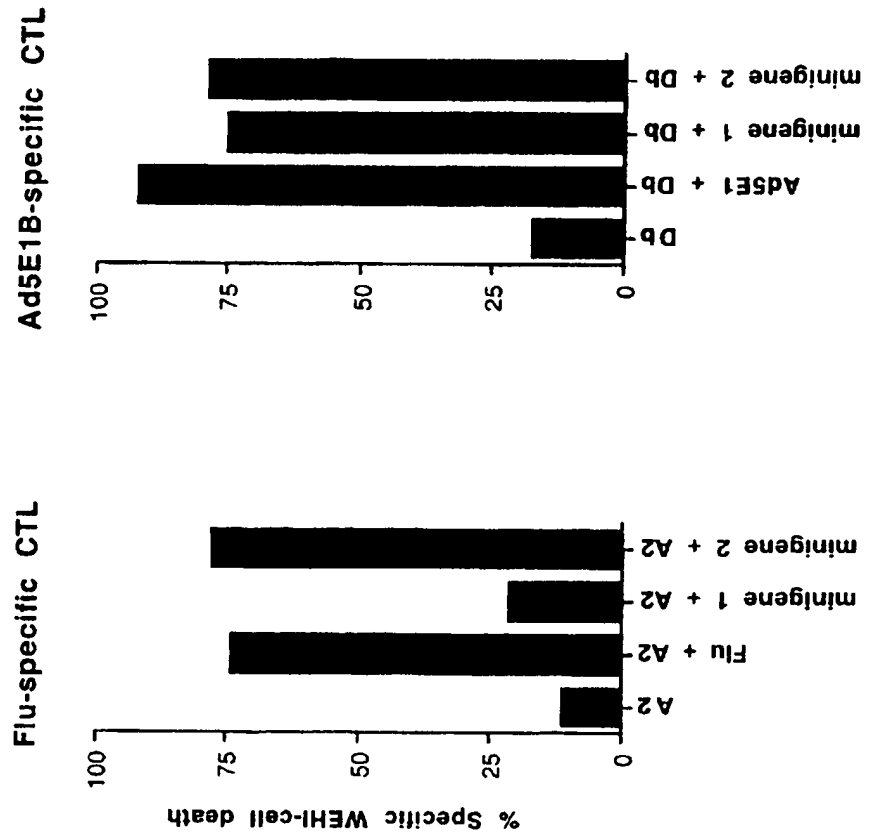


Figure 10

CTL epitopes encoded by rAd in a string-bead fashion
are processed and presented to tumor-specific CTL

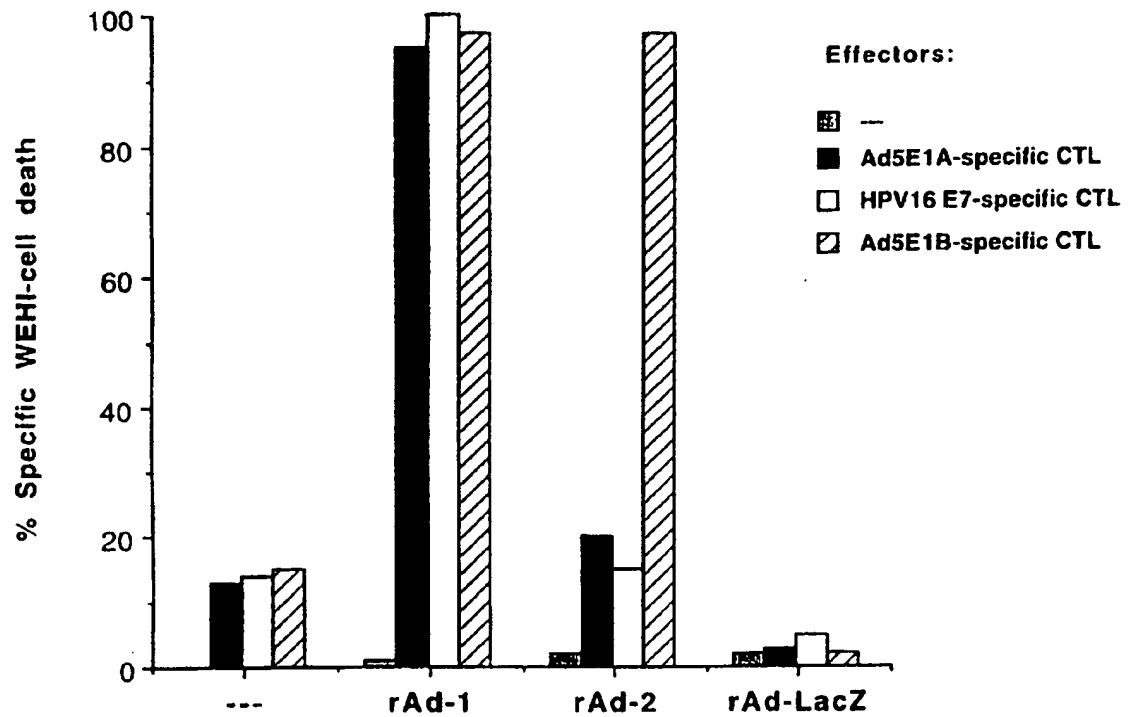


Figure 11

12/14

Ad5E1-specific CTL immunity induced by vaccination with rAd-1 or rAd-2

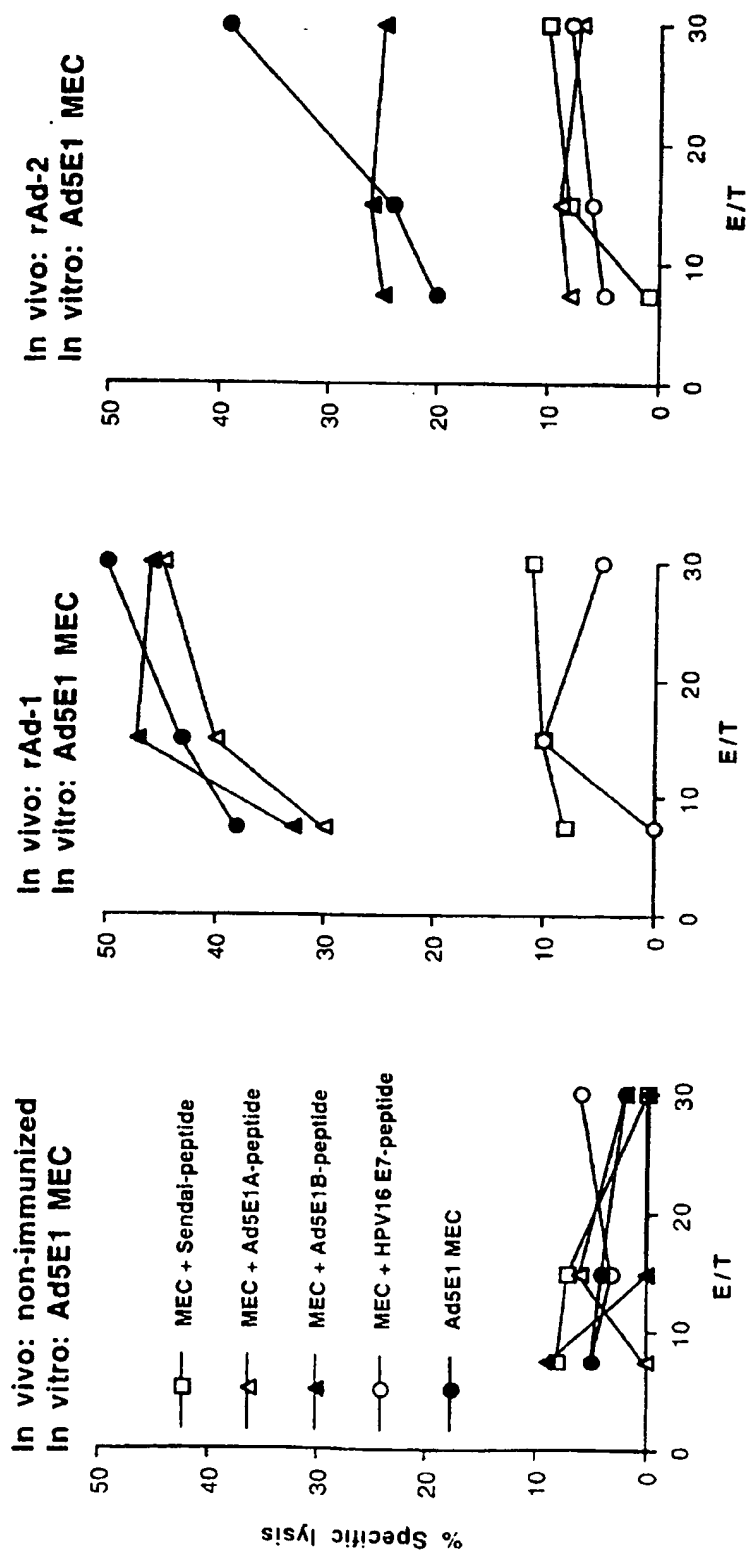


Figure 12

HPV16 E7-specific, H-2^b-restricted CTL immunity induced by vaccination with rAd-1

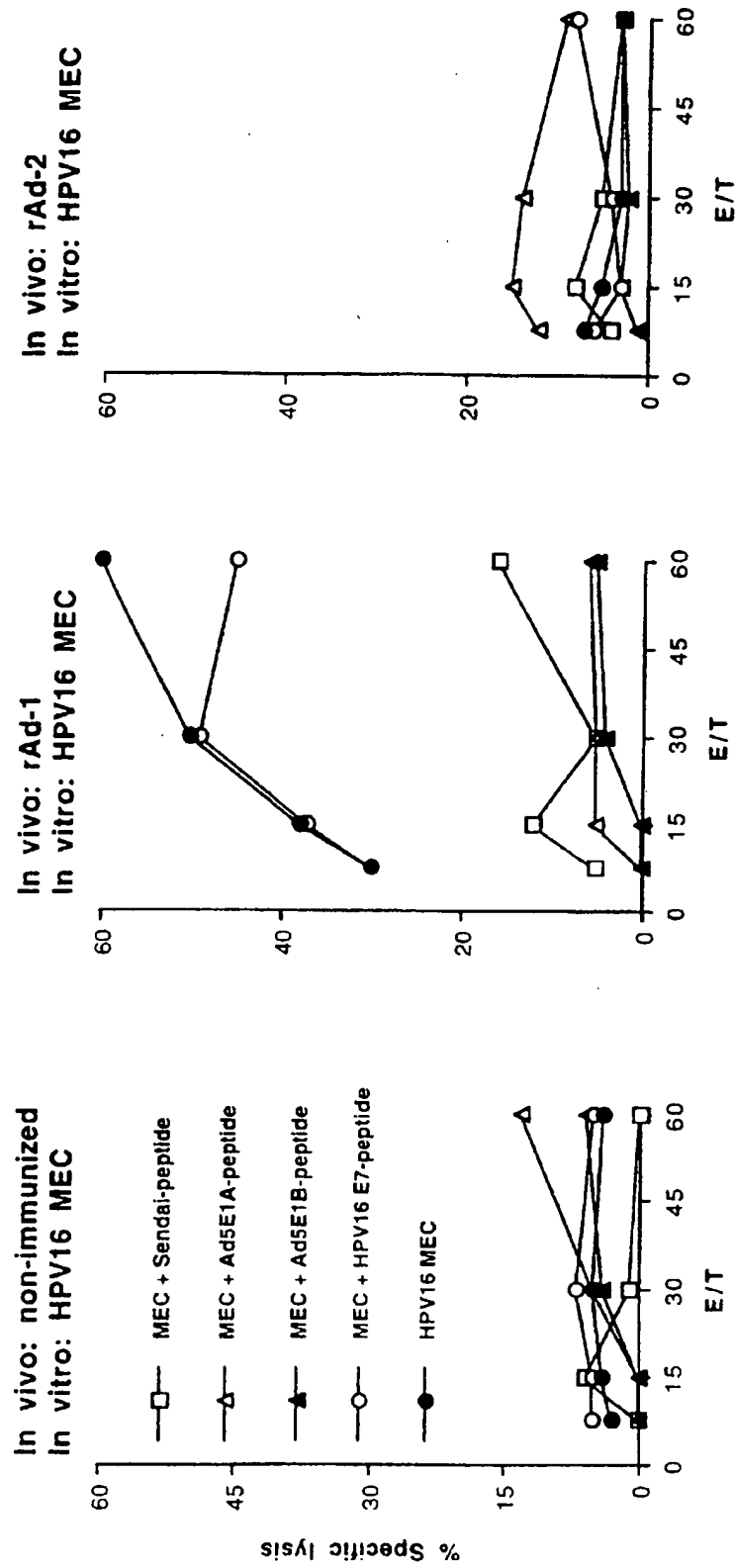


Figure 13

Vaccination with rAd-1 induces protective immunity against Ad5E1A + ras tumors

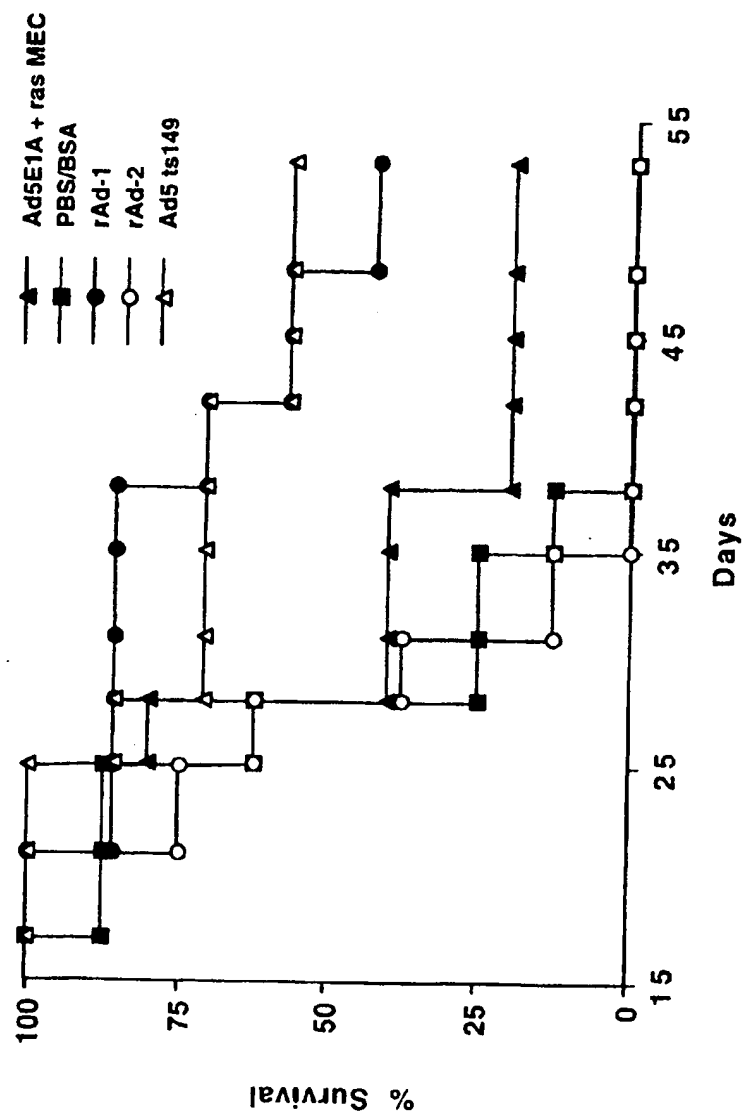


Figure 14

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/NL 97/00229

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 G01N33/569 G01N33/557 A61K39/00 C07K14/00 C12N15/00
C12N15/83

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 G01N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NATURE (LONDON) (1994), 371(6494), 250-2 CODEN: NATUAS;ISSN: 0028-0836, XP000604820 NELSON, CHRISTOPHER A. ET AL: "Peptides determine the lifespan of MHC class II molecules in the antigen-presenting cell" see page 250, left-hand column, line 12 - line 19 see page 250, left-hand column, line 28 - line 32 see page 250, right-hand column, line 1-3 see page 252, left-hand column, line 6 - line 10 see table 2	1-27
X	WO 94 26785 A (US HEALTH) 24 November 1994 see claim 1 --- -/--	20-27

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

8 September 1997

Date of mailing of the international search report

30-09-1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Hoekstra, S

INTERNATIONAL SEARCH REPORT

Internat. Application No.
PCT/NL 97/00229

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	THE JOURNAL OF IMMUNOLOGY, vol. 156, no. 9, 1 May 1996, pages 1308-1314, XP002040034 VAN DER BURG, S.H., ET AL.: "Immunogenicity of peptides bound to MHC Class I Molecules depends on the MHC-peptide Complex stability" see the whole document ---	1-27
P,X	THE JOURNAL OF IMMUNOLOGY, vol. 157, 1996, pages 822-826, XP002039433 THOMSON, S.A. ET AL.: "Recombinant polyepitope vaccines for the delivery of multiple CD8 cytotoxic T Cell epitopes." see the whole document. ---	12-19
X	JOURNAL OF VIROLOGY, vol. 67, no. 1, 1 January 1993, pages 348-352, XP000674226 WHITTON J L ET AL: "A "STRING-OF-BEADS" VACCINE, COMPRISING LINKED MINIGENES, CONFERS PROTECTION FROM LETHAL-DOSE VIRUS CHALLENGE" see the whole document ---	12-19
Y	WO 95 09642 A (LUDWIG INST CANCER RES) 13 April 1995 see page 4, line 16 - page 4, line 30 ---	1-27
Y	JOURNAL OF IMMUNOLOGY, vol. 149, no. 11, 1 December 1992, pages 3580-3587, XP000371892 PARKER K C ET AL: "SEQUENCE MOTIFS IMPORTANT FOR PEPTIDE BINDING TO THE HUMAN MHC CLASS I MOLECULE, HLA-A2" see the whole document ---	1-27
Y	WO 94 21287 A (US HEALTH) 29 September 1994 see the whole document ---	13
E	WO 96 22067 A (UNITED BIOMEDICAL INC) 25 July 1996 see the whole document ---	9-27
A	IMMUNOGENETICS (1995), 42(5), 392-7 CODEN: IMNGBK;ISSN: 0093-7711, XP000603776 DAVENPORT, MILES P. ET AL: "An empirical method for the prediction of T-cell epitopes" see the whole document --- -/--	1-27

INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/NL 97/00229

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ACTA CRYSTALLOGR., SECT. D: BIOL. CRYSTALLOGR. CODEN: ABCRE6;ISSN: 0907-4449, vol. D51, no. 4, 1995, pages 541-549, XP000603826 SCAPOZZA, LEONARDO ET AL: "Molecular dynamics and structure-based drug design for predicting non-natural nonapeptide binding to a class I MHC protein" see the whole document</p> <p>---</p>	1-27
A	<p>MOLECULAR IMMUNOLOGY, vol. 31, no. 11, 1994, pages 813-822, XP000603774 A. SETTE ET AL.: "peptide binding to the most frequent HL-A Class I alleles measured by quantitative molecular binding assays" see the whole document</p> <p>---</p>	1-27
A	<p>JOURNAL OF IMMUNOTHERAPY, vol. 14, no. 2, 1993, pages 121-126, XP002015226 NIJMAN, H.W. ET AL.: "Characterization of Cytotoxic T lymphocyte epitopes of a self-protein, p53 and a non-self-protein, influenza matrix: relationship between major histocompatibility complex peptide binding affinity and immune responsiveness to peptides." see the whole document</p> <p>---</p>	1-27
A	<p>HUMAN IMMUNOLOGY, vol. 43, no. 1, May 1995, pages 13-18, XP000603786 D'AMARO, J. ET AL.: "A computer Program for predicting possible Cytotoxic T lymphocyte epitopes based on HLA Class I Peptide-binding motifs" see the whole document</p> <p>-----</p>	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/NL 97/00229

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9426785 A	24-11-94	AU 7017394 A EP 0701572 A JP 9500614 T	12-12-94 20-03-96 21-01-97
WO 9509642 A	13-04-95	AU 7958994 A	01-05-95
WO 9421287 A	29-09-94	AU 6363094 A CA 2158281 A EP 0692973 A	11-10-94 29-09-94 24-01-96
WO 9622067 A	25-07-96	AU 5849796 A	07-08-96